

Meningoencephalitis and Pneumonitis Due to Western Equine Virus

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WESTERN EQUINE ENCEPHALITIS is defined as a neurotropic virus disease of the nervous system.¹ It is an immunologically and pathologically distinct disease.^{1, 2, 8, 10, 11, 12} The term encephalomyelitis appears to be a misnomer which should be discarded in favor of meningoencephalitis, or just encephalitis;^{3, 5} meningeal involvement was noted in all cases in which autopsy was done in a series herein reported upon, and in all clinical cases there was at least equivocal evidence of meningeal irritation.

Any discussion of the encephalitides *in general* would be completely unrealistic, for the clinical features, sequelae, mortality and etiologic factors are widely variable as between patients and specific disease entities. What is known of encephalitis lethargica for example, does not necessarily apply to Western equine encephalitis; and although poliomyelitis is not often thought of as encephalitis, actually nonparalytic poliomyelitis is a true meningoencephalitis. In the present series of 20 cases only two patients gave a history of localized weakness and in only one was any objective evidence of localized weakness noted clinically. Since clinical evidence of meningitis was present in many cases in the series and myelitis was relatively rare, it is felt that the term Western equine encephalomyelitis should be dropped except in cases in which myelitis is indeed present.

ETIOLOGY

The Western equine encephalitis virus was isolated in horses in 1931 in the San Joaquin Valley by Meyer, Haring and Howitt.⁶ It was isolated in human cases in 1938.¹² The Western equine encephalitis virus is a medium-sized virus and all four of Koch's postulates have been fulfilled in establishing it as an etiologic agent in encephalitis. However, it is clinically indistinguishable from the other encephalitides except for the help given in diagnosis by the known geographical distribution of the encephalitides.

The recently reported California encephalitis virus⁹ is probably only one of several encephalitis viruses which have not yet been isolated. In this

• In a series of 20 cases here presented in a study of Western equine encephalitis, only ten were conclusively proven by serological or histopathological methods, while the other ten were presumptively cases of that disease. Involvement of the spinal cord was of relatively low incidence. In only one case of four in which autopsy was done could the Western equine virus be demonstrated in the cerebral tissues.

There was a rather high incidence of involvement of the respiratory tree. A high proportion of patients had complaints referable to the respiratory tract. Physical signs denoting disease of both the upper and lower respiratory tract, x-ray evidence showing bronchial and pulmonary involvement, and autopsy evidence of bronchopneumonia were noted frequently.

All patients had fever as well as symptoms and physical signs of central nervous system disease. Differential diagnosis posed many interesting and challenging problems.

The clinical features were those of meningoencephalitis and never a "flu-like" syndrome, although in several of the cases diagnosis could not be made with certainty for several days, until meningeal signs developed, and usually the patients were treated with one or several antibiotics during that time.

In all cases in which a neutralization test for the Western equine virus was done, the result was either positive or inconclusive. Results of complement fixation tests were significant in only six cases. In seven of 13 cases in which x-ray films of the chest were made, streaks of increased density were noted.

connection it may be noted that when the author first started summarizing cases from the Tulare County Hospital files during the height of the epidemic of 1952, there were about 30 cases that seemed likely to be later proven Western equine encephalitis. Yet each time the cases were reviewed, the number became smaller. Many of the patients had received antibiotics and it was impossible to be certain on admission whether the condition was a healing bacterial meningitis, nonparalytic poliomyelitis, or encephalitis. Some cases were never clinically distinguished from nonparalytic poliomyelitis. Many of the cases that were excluded from the series were probably encephalitis. A few of the cases that were included may be open to criticism. Finally the series was narrowed down to 20 cases,

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of which only ten were proven beyond shadow of doubt to be Western equine encephalitis.

Finley and Hollister⁵ stated that a proven case of Western equine encephalitis is one in which there is demonstrable antibody titer rise in the patient's blood or the virus is isolated from brain tissue. Hamilton⁸ also expressed the opinion that the diagnosis must rely on complement fixation or neutralization tests. In six cases in the present series, definitely positive titers were shown on serial complement fixations. In the others the complement fixation test results were either negative, inconclusive because of a low or nonrising titer, or were not done because the patient died too soon. In only two cases were the results of neutralization tests definitely positive. In seven other cases the neutralization test was reported as showing antibodies present but in inconclusive amount. In five cases, the neutralization test result was not reported, and in six cases not requested.

At autopsy the virus was isolated from brain tissue by inoculation on a chick embryo in only one case. Unfortunately in the other cases the bodies were embalmed before permission for autopsy could be obtained.

It is obvious that serologic methods are by no means entirely accurate. It is also probable that there are encephalitides for which there are no complement fixation or neutralization tests because the organism has never been isolated.

Lenette and Longshore¹² studied 1,097 cases of infectious encephalitis in California between 1945 and 1950 and noted that in 47 per cent of the cases no known virus could be demonstrated. They also noted that most of the cases of Western equine encephalitis were in Kern, Fresno, San Joaquin and Tulare counties. In most of the cases outside those counties, in patients who had not recently been there, the results of serologic tests were negative. Finley and Hollister⁵ reported a similar observation.

Adams and Weinstein¹ expressed the opinion that the correct diagnosis of encephalitis requires the aid of laboratory methods. Unfortunately, results of laboratory studies in this disease are often more confusing than helpful.

EPIDEMIOLOGY AND PATHOGENESIS

Epidemics in Manitoba, Saskatchewan³ and North Dakota⁷ have been described. Cases have been reported in Illinois.¹¹ In California practically all the proven cases of Western equine encephalitis are from the San Joaquin Valley; it is generally recognized that cases of encephalitis originating in Los Angeles and the San Francisco Bay area are rarely proven serologically to be due to the Western equine

encephalitis virus.⁹ Practically all of the literature pertaining directly to Western equine encephalitis virus is found in CALIFORNIA MEDICINE. Most reports in other journals refer usually to encephalitis in general and are given generalizations about the encephalitides which do not ordinarily apply to each of the specific types.

The Tulare County Public Health Department⁴ reported 32 proven cases of Western equine encephalitis with six deaths in the epidemic of 1952, which corresponds with the present series of 20 cases with four deaths.

Because of the relationship of the disease vector to standing water and mosquitoes, knowledge of geographic features of this area is necessary for an understanding of the problem of health department officers in attempting to control the epidemic. The Central Valley of California is a completely land-locked valley approximately six hundred miles long and varying from fifty to a hundred miles in width. The mountains protect the area from all the lower nimbus clouds so that the weather is exceptionally mild, especially in the San Joaquin, which is the southern half of the valley. Rainfall is scant. The entire Valley is now a network of irrigation ditches. The principal product of the area is cotton and irrigating it entails the flooding of huge areas of land. Any dip in a field can hold water for some time. In warm weather, the *Culex tarsalis* and *Aedes aegypti* mosquito can develop from the egg to the adult stage in about four days. These factors combine to make an almost insurmountable problem for the local health departments and mosquito control districts.

According to Lenette and Longshore,¹² even though cases of encephalitis are reported throughout the year, laboratory-confirmed cases of encephalitis are found only in July, August and September, and the serologically negative cases are probably due to a yet undiscovered virus. Of the 20 cases in the present series, all but two occurred between the beginning of June and the end of September. One was in April and one in October. Not until after the first of July was the first case in the series diagnosed—at autopsy; and the last diagnosis was made on a patient admitted to Tulare County Hospital on the second of September with a complement fixation of significant titer. The first case reported in our series did not have complement fixation and neutralization tests were not done in the first case in the series, for encephalitis was not being considered at that time. It is worth noting that there were many other cases of possible and probable encephalitis during the height of the epidemic, but not so diagnosed.

Table 1 shows the incidence in this series by sex, race and age. The ratio of male to female patients

TABLE 1.—Incidence of Western Equine Encephalitis by Sex, Race and Age in 20 Cases

Sex		Race		Age							
M	F	White	Mexican	Under 1 yr.	1 to 10	10 to 20	20 to 30	30 to 40	40 to 50	50 to 60	60 to 70
16	4	85%	15%	4	3	2	2	3	3	2	1

was 4:1. In other reported series¹² the ratio was 2:1. It has been suggested that the sex difference is owing to women's presumably lesser exposure to mosquito bites (since they are, in general, outdoors less); but in the area of this study, that may not be a very large factor, for a large proportion of the female population is employed in agricultural work in the open.

Three of the patients were of Mexican extraction, the remainder Caucasian. General hospital and clinic patients in the area are about evenly divided between the two races.

It is generally conceded that Western equine encephalitis is a disease of man and horse which occurs mainly in the Central Valley of California. It is less generally accepted that man and horse are only accidental hosts.⁵ The *Aedes aegypti* and *Culex tarsalis* mosquitoes are the vectors of this disease.^{2, 5, 6}

One of the main missing links in epidemiology is in the identification of the reservoir. Although some believe that the horse is the reservoir, the preponderance of evidence points to an avian reservoir. The domestic fowl has been proven to be a short-term reservoir, and the chicken mite has been suspected but not completely incriminated in epidemics, even though the virus has been found in the mites.¹⁰ The encephalitis virus is not passed from man to man, from horse to horse or from horse to man. In Kern County, California, and Yakima Valley, Washington, some wild birds have been proven to be hosts and their nests have been found to be infested with various species of arthropods that transmitted the Western equine virus.¹⁰ The life cycle of the virus is complex and not understood. It is felt that spinal fluid, blood, pharyngeal washings and feces are useless for isolating the virus under present methods, and only brain tissue from autopsy material has been found to yield the virus with any degree of regularity. However, the recently described technique of obtaining positive blood cultures for the poliomyelitis virus gives some encouragement.¹⁶

The virus has been isolated from mosquito pools frequently in early summer by the California State Department of Public Health's Encephalitis Study Unit.

It is generally accepted that the disease is transmitted from bird to man, or from bird to horse, by the mosquito vector. When the mosquito bites the

accidental host, the virus finds its way to the central nervous system—whether through the blood stream or by migration along the peripheral nerves is not known. The exact incubation period in man is very uncertain. How the virus finds its way to the respiratory tract is also uncertain, but it would seem more plausible that the vascular system carries the disease to the respiratory tract, rather than that there is a migration along the nerves. Recent work demonstrating a true viremia in poliomyelitis lends weight to this concept.¹⁶ The isolation of the lymphocytic choriomeningitis virus from the blood of patients during the acute disease also bolsters the theory.¹⁷

CLINICAL AND PATHOLOGIC FEATURES

In almost all cases in the series meningeal involvement was noted either clinically or at autopsy. Two of the patients complained of cough and two had positive pulmonary findings; five had symptoms compatible with involvement of the upper respiratory tract. X-ray films of the chest were done in 13 cases and in seven of them there was very definite evidence of pulmonary involvement. Radiographically there seemed to be a predilection for the right lower lobe, although other parts of the lower respiratory tract were also involved.

Autopsy was done in four cases. In one, only the head was examined. Bronchopneumonia was present in two of the other three cases, as was myocarditis. In one case a chromophobe adenoma of the pituitary (doubtless unrelated to the viral disease) was observed. Examination of the spinal cord was done in only one case, and edema only of the lateral and anterior horns was noted. The ganglia themselves appeared normal microscopically.

Examination of the autopsy summaries in these cases might lead one to conclude that the bronchial pneumonia noted in two cases was of a terminal nature. However, in light of the rather high incidence of respiratory signs and symptoms plus positive radiological evidence of pulmonary involvement in other cases in the series, it would seem more logical to assume that the pulmonary involvement noted at autopsy was due to a primary inflammatory response to the Western equine virus (Figure 1). It is noteworthy that the lymphocytic choriomeningitis virus was found in consolidated lung tissue in one fatal case of lymphocytic choriomeningitis.¹⁷

The autopsy summary of one case, in which the

lungs were normal, described an acute myocarditis with minute epicardial petechiae. The latter can be a manifestation of terminal hypoxia or of a possible terminal sepsis.¹⁵ In view of the known generalized nature of the disease, one might wonder—only in conjecture, of course—if the conditions noted could have been due to an acute viremia resulting from the Western equine virus.

As the author was not aware of the myocardial complications of some of the other encephalitides¹⁷ at the time the patients were being treated, routine electrocardiograms for evidence of myocarditis were not done.

SYMPTOMATOLOGY

The symptoms of Western equine encephalitis are primarily those of an inflammatory disease of the central nervous system. Since the lesions may be scattered throughout the nervous system¹ the symptoms can be quite varied. Finley and Hollister⁵ reported a uniform distribution of the disease in ages six months to 60 years, which corresponds with our data in the present series. They also noted that in adults there are more males affected than females, and in children the sexes were equal. Fever, headache, lethargy, drowsiness and stiff neck were the most common symptoms during the first three days of the illness. One-third of adults were reported to have tremor, while in children convulsions were quite common. These data also coincide with observations in the present series.

Kohut¹¹ reported a case in which the primary complaint was looseness of stools. Upon physical examination, drowsiness, plucking movements of the fingers, rigidity of the extremities, pharyngitis and diffuse abdominal tenderness were noted. Kohut said that a "flu-like" syndrome is present in all encephalitis. Although symptoms of involvement of the respiratory tract were present in a high proportion of the cases in the present series the symptomatology was more that of a central nervous system disease than of respiratory. Although rigidity and choreiform movements are reported to be common in other types of encephalitis, with the exception of nuchal rigidity, these conditions were rarely observed with Western equine encephalitis in the present series. A fairly sudden onset is common in children;² usually it is more insidious in adults.

History-taking was extremely difficult in this series, for many of the patients were brought in and left by the local police, by a helpful neighbor or by an employer and were unable to give a history. Many of the patients were migratory agricultural laborers, and many had no immediate family available. Follow-up observation also was almost impossible for the same reasons.

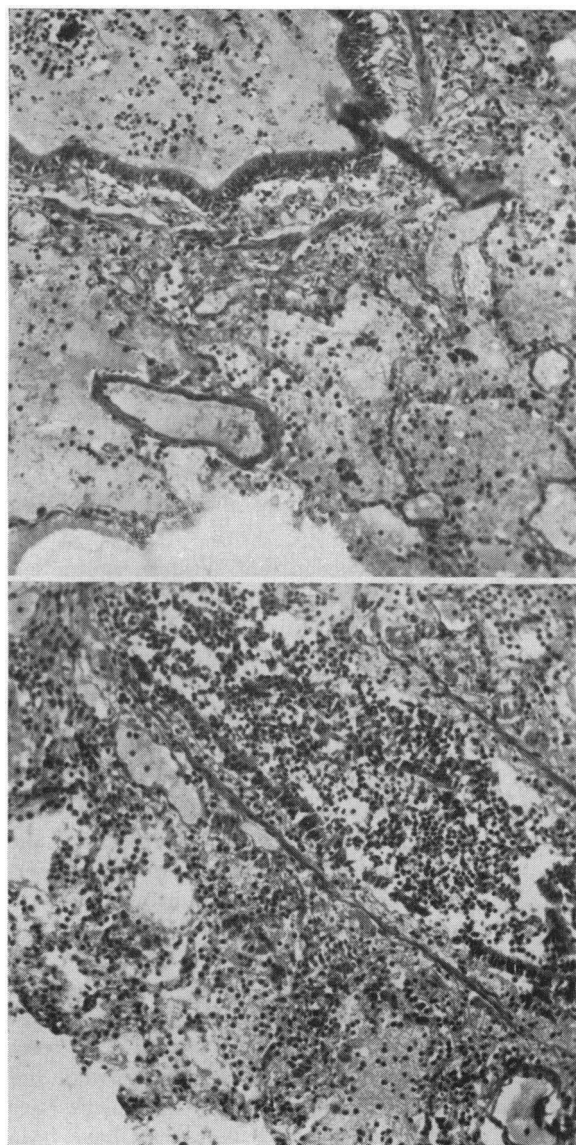


Figure 1.—Sections of lungs in which were noted bronchi filled with polymorphonuclear leukocytes and many alveoli filled with red blood cells and polymorphonuclear leukocytes.

The severe sequelae that are seen commonly in the other encephalitides are more the exception than the rule in Western equine encephalitis. There were none in the few cases in the present series in which follow-up was done.

Fulton and Burton,⁷ reporting on observation of 550 cases in Saskatchewan in 1941, noted that the symptoms were often confused with a "flu-like" syndrome, but that sequelae, which would occur some time after the acute infection, were proven by neutralization tests to be due to Western equine virus.

In the present series the main complaints (Table 2) were referable to the central nervous system

and all patients had complaints that were directly referable to the brain. This is very striking inasmuch as the numerical term *100 per cent* has such a small applicability to medical statistics—even in small series.

Fever was the most common complaint. Although a history of fever was elicited in only 60 per cent of the cases, all patients were found to have fever upon examination.

Headache was a very common symptom but varied quite a bit in character in cases in which a description of it could be elicited.

It is interesting that at least equivocal nuchal rigidity was noted in 85 per cent of the cases on physical examination. The complaints of cough and earache are of interest when correlated with the physical findings referable to the respiratory tract.

As 35 per cent of the patients had previously received antibiotics to which they had not responded, an extremely difficult problem in diagnosis was raised, for the clinical and spinal fluid determinations in these cases would fit the clinical picture of either a viral disease of the central nervous system or a healing purulent meningitis. To withhold antibiotics in a purulent meningitis would be unnecessarily risking the patient's life. On the other hand, continuing antibiotics in a case of Western equine encephalitis would not only have no effect on the disease but would further cloud the diagnosis by foreclosing the opportunity of carrying out a therapeutic trial. In looking back over the cases which were excluded from the present series because of treatment with antibiotics, it is felt that some lives were probably saved by continuing antibiotic therapy.

SIGNS

Physical signs (Table 3) were a much more reliable index of diagnosis in the present series than were case histories. In all cases there was elevation of temperature ranging from 99.8°F. to 106.0°F. on admission. In all cases there were physical signs of central nervous system disease. Seventeen patients had nuchal rigidity. In the three cases in which nuchal rigidity was not present the patients died. Of the four comatose patients, three were in coma on admittance and the other became comatose afterward. All died.

It is felt that the rather high incidence (35 per cent) of positive physical findings referable to the respiratory tract may be significant, especially in view of the high incidence of respiratory tract involvement in lymphocytic choriomeningitis (20 per cent), mumps meningitis (13 per cent), and leptospiral meningitis (33 per cent).¹⁷

TABLE 2.—Incidence of Various Complaints and Symptoms in 20 Cases of Western Equine Encephalitis

Complaint or Symptom	No. Cases	Per Cent
Lethargy	4	20
Coma	3	15
Confusion	7	35
Delirium		
Disorientation		
Dizziness	2	10
Irritability	2	10
Convulsions	5	25
Fever	12	60
Headache	9	45
Malaise	6	30
No response to previous antibiotics	7	35
Stiff neck	7	35
Vomiting	5	25
Coughing	3	15
Head trauma	2	10
Localized weakness	2	10
Earache	3	15

TABLE 3.—Incidence of Various Signs of Western Equine Encephalitis in 20 Cases

Highest temperature	106.0° F.	
Lowest temperature	99.8°	
Average	102.8	
	No. Cases	Per Cent
Nuchal rigidity	17	85
Disorientation	5	25
Coma	4	20
Lethargy	2	10
Twitching	4	20
Choreiform movements		
Shakiness		
Babinski's sign	3	15
Absence of deep tendon reflexes....	4	20
Hyperactive deep tendon reflexes..	1	5
Localized weakness	1	5
Rigidity	1	5
Hamstring spasm	2	10
Pupils irregular	1	5
Bulging fontanelle	2*	10
Pulmonary findings	2	10
Pharyngitis, tonsillitis or otitis media	5	25

* Three of the patients in the series were infants.

That so few patients had reflex changes indicating spinal cord involvement indicates that this disease is not primarily myelitic.

After reviewing the data on suspected cases a number of times, the author has come to the conclusion that a positive diagnosis of Western equine encephalitis is almost impossible upon initial examination even at the height of an epidemic. It can also be concluded that a negative result of a complement fixation or neutralization test does not rule out encephalitis and diagnosis can best be made by reviewing the patient's chart months after he has left the hospital. In many typical cases results of complement fixation tests were negative and neutralization tests inconclusive. In many cases thought to be nonparalytic poliomyelitis, results of complement

fixation and neutralization tests were positive. A number of patients who were thought on admission to have typical cases of Western equine encephalitis, were later proved at autopsy to have granulomatous meningitis. Therefore, if the cases of granulomatous meningitis and the cases in which the patient had already received antibiotics be disregarded, it would seem that a diagnosis of encephalitis would be easy except for the fact that complement fixation and neutralization tests do not always distinguish what type of encephalitis is present.

LABORATORY, RADIOGRAPHIC AND CLINICAL OBSERVATIONS

Data on laboratory, roentgenographic and clinical observations were as follows:

Blood: The number of leukocytes varied from 6,250 to 16,500 per cu. mm.—in most instances in the range of 12,000. The proportion of segmented neutrophils varied from 31 per cent to 83 per cent, with a mean of 61 per cent; the proportion of stabs from 0 to 35 per cent with a mean of 10 per cent, and of monocytes from 0 to 13 per cent with a mean of 3 per cent.

Urine: Urinalysis was recorded in all but two of the 20 cases. In seven, definite abnormalities were noted. One patient had 4+ albumin with gross blood, one had 4+ albumin with a few leukocytes, two had positive reaction for albumin and both erythrocytes and leukocytes, two had leukocytes only and one had albumin only. It is noteworthy that not all patients with hyperpyrexia had abnormalities in the urine, nor was there any correlation of urinary abnormality with any of the other data in each case or with clinical progress. Three of the patients with urinary abnormalities were over the age of 50, and in them the condition may not be relatable to the disease; but three were under 30 years of age.

Spinal Fluid: Spinal fluid pressure was not determined in all cases, partly because of the difficulty in holding the disoriented patients still during the spinal tap and partly because there were not enough manometers available owing to the greatly increased need in an epidemic situation.

The spinal fluid cell content varied from 67 to 600 per cu. mm., with the exception of one case in which there were 9 cells per cu. mm. The mean cell count for all cases was 248. The proportion of polymorphonuclear cells varied from 5 per cent to 89 per cent, with a mean of 36 per cent. Early in the epidemic the polymorphonuclear cells predominated, but late in the epidemic the mononuclear cells predominated at the time of admittance to hospital. There appeared to be no correlation be-

tween the number of cells in the spinal fluid and the differential proportions; nor was there any correlation between these factors and the results of the complement fixation and neutralization tests for the Western equine virus.

The spinal fluid protein content in most cases was at the top of the normal range, although the variation was great, ranging from 15 mg. to 102 mg. per 100 cc. The spinal fluid sugar content, however, was slightly high in most cases, but the determinations were not done concurrently with blood sugar determinations.

There was growth of organisms on spinal fluid cultures in three cases, but a different organism in each case and not the Western equine virus in any of them. It was assumed that these were contaminants.

Serological tests for Western equine encephalitis: Seven patients, including the first four and the last in the series, had no serological tests for the Western equine virus. Three of the seven were patients who died. In seven cases antibody was absent or present in insignificant amount as shown by the complement fixation test, while in six cases there was a significant rise in titer on serial tests ten days apart. In four of the latter, however, results of neutralization tests, were inconclusive, and in only two cases was the result positive. All of the cases in which the result was negative or insignificant for complement fixing antibody also had neutralization tests that were interpreted by the California State Department of Public Health Laboratory as being inconclusive either due to small amounts of neutralizing factor or failure to show a significant rise on serial tests ten days apart. None of the neutralization tests were negative for Western equine infection.

It is obvious from the clinical features in the present series that encephalitis cannot be ruled out on the basis of negative or inconclusive results of blood tests. If the complement fixation and neutralization tests for the Western equine virus are as accurate as they purport to be, then it must be concluded that some of the cases in the present series were due to some as yet unknown virus or viruses which have not been isolated and for which no serological test has been developed. Negative results of complement fixation and neutralization tests, then, may rule out Western equine encephalitis, but do not rule out encephalitis due to other viruses. In all cases results of serological tests were negative for St. Louis and mumps encephalitis.

Radiological Findings: In a review of the literature no mention could be found of pulmonary involvement by the Western equine encephalitis virus, even though many of the encephalitides start out as a "flu-like" syndrome. In seven of the 13

cases in the present series in which x-ray films of the chest were made, positive radiological evidence of involvement of the lower respiratory tract was noted. No abnormality was observed in the other six. The physical findings and autopsy findings are consistent with the x-ray findings of streaks of increased density extending outward from the hilum and usually in the right lower lobe. It has been noted that abnormalities in the lungs have been observed roentgenographically in Japanese encephalitis,¹⁴ mumps meningitis, and leptospiral meningitis.¹⁷ Streaks of increased density in the upper left lung field were seen in x-ray films of one of the patients. In that case complement fixation was positive for the Western equine virus in the dilution of 1:128 and the result of a neutralization test was inconclusive.

Course of the Disease: Each patient was ill from one to five days—average about three days—before being hospitalized. The temperature became normal usually on the third hospital day, but as early as the first day and as late as the ninth. Cerebration, however, did not return to normal quite so early and the period of hospitalization necessary for the spinal fluid and cerebration to return to normal varied from five to 21 days, with a mean and median of 14 days. During this time the patient seemed to be oblivious to his surroundings. Often the patient would complain of stiff neck or even of being “sore all over” for seven to ten days after admission. Patients with the latter complaint were included in this series only if results of complement fixation or neutralization tests were positive or if a thorough examination of muscles had been done by a physical therapist and no evidence of localized weakness found.

Three of the four patients who died were comatose when admitted and the other became comatose

one day after admission. Two died the day of admission, one on the second hospital day, and one on the seventh day.

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